IN THE CLAIMS:

Please amend independent claim 90 as follows:

At line 2, after the term "product of" delete "a" and insert therefor --an intact--.

REMARKS

The Examiner indicated that the title is "not descriptive" and required a new title. Accordingly, Applicants have amended the title to more particularly specify that the "Immunogenic Conjugates" are conjugates of the capsular polymer of *S. pneumoniae* and a toxin and toxoid. It is respectfully submitted that this amended title succinctly describes the presently claimed subject matter.

Claims 90, 91 and 93-97 are currently under active consideration. Independent claim 90, as well as all claims dependent thereon, has been amended to recite that the claimed cross-linked conjugates comprise a reductive amination product of an intact capsular polymer of *Streptococcus pneumoniae* having at least 2 carbonyl groups attached to amine groups of a bacterial toxin or toxoid. These claims, as amended, are fully supported by the specification and claims as originally filed, particularly by the specification at page 2, lines 9-16 and in Example 11 at pages 50-51.

I. Rejections Based on Jennings Alone or In Combination With Uchida

Claims 90 and 96 remain rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 4,356,170 to Jennings et al. (Jennings). Claims 91 and 93-95 remain rejected under 35 U.S.C. §103 as obvious over Jennings and claim 97 remains rejected under 35 U.S.C. §103 over Jennings in combination with Uchida et al., 1972, Science

115:901-03 (Uchida). The Examiner insists that the presently claimed cross-linked conjugates having "at least two carbonyl groups" are inherent in the teachings of Jennings, citing col. 2, line 44 of Jennings. Although the Examiner agrees that Jennings teaches the use of mild oxidation conditions, the Examiner contends that Jennings "teach[es] cross-linked polysaccharide to immunogenic conjugates as vaccines". Uchida is applied in combination with and "as a functional equivalent to the carrier" of Jennings.

With all due respect to the Examiner, Applicants respectfully urge that the Examiner's contention that the presently claimed conjugates having at least two carbonyl groups which are necessarily cross-linked conjugates are "inherent in the teachings of Jennings" is plainly wrong, both as a matter of fact and law. For reasons set forth more fully below, it is respectfully requested that the Examiner reconsider her reliance upon the Jennings reference which is plainly misplaced.

Firstly, as detailed by Applicants in their previous response, the Jennings reference teaches conjugation via a single aldehyde group on the end of the polysaccharide. The clear focus of Jennings is to generate a single aldehyde group. This is accomplished by Jennings by pretreatment of a capsular polymer or polysaccharide which otherwise would yield more than one aldehyde, so that upon treatment with periodate, only one aldehyde is obtained. See, Jennings at col. 3, lines 10-17, 22-27, and at col. 4, lines 49-59 (pretreatment of the meningococcal group A polysaccharide).

In addition, Jennings also teaches mild oxidation of the polysaccharide in order to selectively form only a single terminal aldehyde group. Jennings at col. 3, lines 28-39. See Jennings, at col. 5, lines 38-54 which specifically teaches mild periodate conditions so as to produce only a single aldehyde on the polysaccharides of meningococcal C group. See also, id. col. 6, lines 5-9.

Moreover, according to the clear teaching of Jennings, the method of attachment is specific in that the only covalent attachment between the toxoid and the capsular polysaccharide occurs at the single terminally located aldehyde group of the polysaccharide (Jennings, at col. 3, lines 55-63; see also, id. at col. 2, lines 34-38. Jennings further asserts that the method of coupling employed "avoids cross-linking" between the polysaccharide and the protein. Jennings at col. 2, lines 38-39; see also, id. at col. 3, lines 62-63. Finally, as specifically recited in the claims of the Jennings patent, the conjugates prepared as taught therein are "non-cross-linked" conjugates. E.g., independent claims 1 and 11.

Thus, there is no affirmative teaching in Jennings concerning cross-linking. Rather, in complete contrast to the present conjugates which are specifically designed to be cross-linked conjugates, the only teaching in Jennings about cross-linking is a very negative view which clearly teaches away from cross-linking.

Secondly, as detailed below, the Court of Appeals for the Federal Circuit (CAFC) which recently considered the scope of the teaching of Jennings has emphatically rejected the Examiner's interpretation of Jennings. Examiner's attention is directed to the opinion of the CAFC in North American Vaccine, Inc. v. American Cyanamid Company, No. 93-1076 (October 6, 1993), a copy of which is attached hereto as Exhibit A. In North American Vaccine, the CAFC considered the validity and scope of the claims of U.S. Patent No. 4,356,170, i.e., the Jennings reference relied upon by the Examiner.

More particularly, in North American Vaccine, the CAFC carefully considered whether conjugates, such as presently claimed, having at least 2 carbonyls and by means of which, when coupled to an amine group of a bacterial toxin or toxoid, end-to-end cross-linked conjugates are formed, were within the scope of the teaching (and

hence the claims) of Jennings. In construing the language of Jenning's claims, the Court considered not only the language itself but also the teaching of the Jennings specification, and emphatically concluded that it found "no indication in the patent specification that the inventors intended to include end-to-end linkages within the scope of their invention." North American Vaccine, at page 9[1]. The Court noted that "[a]ll references to polysaccharide linking speak of a linkage, not multiple linkages." Id. In particular, the Court quoted the teaching of Jennings, at col. 2, lines 33-37 which reads:

> We have found it possible to introduce a free aldehyde group into the polysaccharide molecule at a terminal location and to specifically couple this aldehyde group to protein without activating other functional groups on the polysaccharide. (emphasis in original).

Id. Additionally, the Court noted that all the examples support only linkage at one terminal, thus, precluding cross-linked conjugates. Id. at page 10.

Finally, the Court concluded that the Jenning's teaching of linkage "to a terminal portion" includes only conjugates in which there is a bond between the protein and the polysaccharide at one end, i.e., monofunctional linkage, and that the teaching excluded conjugates in which there was other than monofunctional linkage, including end-to-end cross-linking as presently claimed. Id. at page 14.

Thus, the Court's determination completely supports Applicants' position that nothing in Jennings would have suggested, much less taught, the present cross-linked conjugates. Jenning's teaching of avoiding cross-linking cannot be interpreted to suggest conjugates in which cross-linking is an integral feature. Examiner is respectfully

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[1] Similarly, the District Court in North American Vaccine Inc. v. American Cyanamid Co., 24 U.S.P.Q.2d 1898, 1902 (S.D.N.Y. 1992) had concluded that: "there is nothing in this [Jennings] patent affirmatively teaching anything about achieving cross-linking. There is nothing in the patent except a negative view of cross-linking." (emphasis added). For Examiner's convenience, a copy of this district court opinion is attached hereto as Exhibit B.

requested to reconsider and withdraw her rejections based on Jennings either alone or in combination with Uchida.

II. Rejections Based on Anderson and Clements

Claims 90, 96 and 92[sic] have been rejected under 35 U.S.C. §102(f) as anticipated by U.S. Patent No. 4,808,700 to Anderson and Clements (Anderson and Clements). Claims 91 and 93-95 have been rejected under 35 U.S.C. §103 as obvious over Anderson and Clements. The Examiner alleges that the presently claimed invention is taught at cols. 29-32, Sections 6.5 and 6.6 of Anderson and Clements and further that "substitution of various serotypes of S. pneumoniae" in the conjugates would have been clearly obvious to one of skill in the art.

Applicants emphatically disagree and submit that nothing in the teaching of Anderson and Clements suggests, much less anticipates, the presently claimed conjugates. As indicated above herein, independent claim 90 (as well as all the remaining claims which are dependent on claim 90) has been amended to more precisely specify that the presently claimed immunogenic cross-linked conjugates comprise an intact capsular polymer of *S. pneumoniae*, having at least 2 carbonyl groups, covalently attached to a bacterial toxin or toxoid to form a cross-linked conjugates.

In complete contrast to the present conjugates which comprise an intact capsular polymer, the conjugates taught by Anderson and Clements necessarily contain a capsular polymer fragment. A careful review of Sections 6.5 and 6.6 at cols. 29-32 of Anderson and Clements cited by the Examiner reveals that the conjugates exemplified therein contain capsular polymer fragments, not intact capsular polymer. Section 6.5, entitled "Conjugation of Capsular Polymer Fragments of Streptococcus Pneumoniae to

CRM_{197}" (emphasis added) describes the preparation of "capsular polymer fragments [made] from the Sp. 6 capsular polymer by selective acid hydrolysis and [conjugation] to CRM_{197}." As shown in the Table at col. 3, lines 18-24, the hydrolyzed polymer fragments used had a ratio of total hexose/reducing hexose of 6.5 whereas the intact Sp. 6 capsular polymer had a value of 350. Such different ratios clearly indicate significant difference in the degree of polymerization of the intact capsular polymer presently used and the capsular polymer fragments of Anderson and Clements. Similarly, Section 6.6 entitled "Production of PRP-Conjugate Vaccines by Periodate Oxidation", describes the preparation of capsular polymer fragments of polyribosyl ribitol phosphate (PRP), the capsular polymer of *Haemophilus influenzae* type b, by periodate oxidation and conjugation of fragments having a desired low degree of polymerization (DP) to diphtheria toxoid.

As shown in Table 11 at col. 32, lines 28-38 and Table 12 at col. 32, line 55 through col. 33, line 12, all the PRP fragments used in the conjugates had degrees of polymerization (DP) of 10 or 20. DP for such PRP fragments is equal to:

$$DP=\frac{TotalRibose}{ReducingRibose}\times 2.$$

Thus, the ratio of Total Ribose/Reducing Ribose for these PRP fragments is 5 or 10. As shown in Tables 1 and 2 at col. 19, lines 17-23 and lines 48-56, such PRP fragments are classified as small (S) or, at most, medium (M) sized PRP fragments which differ significantly from the entire or intact PPR capsular polymer which has a ratio of Total Ribose/Reducing Ribose of 493.

Most importantly, however, it is clear that the teaching of Anderson and Clements, as a whole, is directed to the preparation of conjugates in which a capsular polymer fragment, not an intact capsular polymer, is used. Examiner's attention is directed to the teaching of Anderson and Clements, particularly the Summary of the invention at col. 7, lines 58-61 which reads: The present invention relates to the covalent attachment of capsular polymer fragments derived from bacterial capsular polymers to bacterial toxins, toxoids or binding subunits by means of reductive amination." (emphasis added). Again at col. 8, lines 27-42, Anderson and Clements explains that:

> Finally, the immunogenic conjugates of the invention contain fragments of capsular polymers, not intact capsular polymers. The highly repetitive structures of capsular polymers [CP] may be in part responsible for their failure to expand the capacity for antibody production in infants.
>
> A conjugate of intact (highly polymerized) CP and protein may only partially overcome the immunologic disadvantages of CP alone.
>
> On the other hand, the use of capsular polymer fragments may circumvent the disadvantages of the repetitive structure. Additionally, the CP determinants of a conjugate having CP fragments are on the average closer to the carrier than are the CP determinants of conjugates having intact CP, and this proximity of carrier may be necessary for a more effective "carrier effect." (emphasis added).

See also, the Detailed Description of Anderson and Clements at col. 9, lines 52-56 (conjugates of the invention are formed by reacting a reducing end group of a capsular polymer fragment to an amine of a toxin or toxoid) and the description of the antigenic capsular polymers fragments at col. 9, line 59 through col. 10, line 9. Finally, all the Examples of Anderson and Clements demonstrate the preparation of conjugates containing only capsular polymer fragments, not intact capsular polymers.

In summary, unlike the present conjugates containing an intact capsular polymer, i.e. a polysaccharide, the conjugates of Anderson and Clements contain a capsular polymer fragment having a low DP, i.e., an oligosaccharide.

Moreover, there is no affirmative teaching in Anderson and Clements to prepare conjugates, as presently claimed, containing an intact capsular polymer. Rather, the only teaching concerning intact capsular polymers in negative (see especially, col. 8, lines 27-42). As affirmed by the Court of Appeals for the Federal Circuit, such negative teaching, which in fact teaches away from the presently claimed invention, is highly probative of the non-obviousness of the claimed invention. E.g.; Raytheon Co. v. Roper Corp., 724 F.2d 957, 961 (Fed. Cir. 1983), cert. denied, 469 US. 835 (1984); accord, Dow Chemical Co. v. U.S., 18 U.S.P.Q.2d 1657, 1662 (Ct. Cl. 1990); In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986).

In view of the above amendments and remarks, it is respectfully submitted that the rejections based on Anderson and Clements are clearly improper and/or have been overcome and should be withdrawn.

III. Rejections Based on Double Patenting

The Examiner has maintained the rejection of claims 90, 91 and 93-97 under the judicially created obviousness-type double patenting in view of:

(1) U.S. Patent No. 4,673,574 to Anderson (Anderson I), claims 1-44 and 50;

(2) U.S. Patent No. 4,761,283 to Anderson (Anderson II), claims 1-27, 30 and 31;

(3) U.S. Patent No. 4,808,700 to Anderson and Clements (Anderson and Clements), claims 1-8;

(4) U.S. Patent No. 4,902,506 to Anderson and Eby (Anderson and Eby I), claims 1-32; and

(5) U.S. Patent No. 5,097,020 to Anderson and Eby (Anderson and Eby II), and claims 1-34.

Additionally, the Examiner has maintained the provisional double patenting rejection of claims 90, 91 and 93-96 in view of claims of Application Serial No. 07/205,132 by Anderson and Clements (Anderson and Clements Application).

The Examiner alleges that "all of the related patents and application are drawn to cross-linked immunogenic conjugates wherein the polysaccharides are oxidized to provide at least two carbonyls."

Applicants do not agree and in no way acquiesce to the Examiner's arguments or rejections. However, in order to advance the prosecution of the present claims, the Assignee of Anderson I and II and of Anderson and Eby I and II, co-assignee of the present application by Anderson and Eby provides herewith a terminal disclaimer disclaiming any portion of any patent issuing on the present application which would extend beyond the expiration date of any of these earlier issued patents.

With regard to the cited Anderson and Clements Patent and the co-pending Anderson and Clements Application, for reasons detailed above herein, it is clear that the subject matter of the present application is not an obvious variation of the claims of these references since the teaching of Anderson and Clements is clearly away from the use of intact capsular polymers as presently claimed. The present claims have been amended to more clearly recite that they are directed to compositions in which an intact capsular

polymer is attached to a toxin or toxoid, resulting in a cross-linked conjugate. The cited Anderson and Clements Patent (or Application) does not suggest preparation and use of such conjugates.

Accordingly, in view of the above amendments, remarks, and the submitted terminal disclaimer, it is submitted that the rejections based on obviousness-type double patenting have been avoided and should be withdrawn.

IV. Conclusion

In light of the above amendments and remarks, it is submitted that the claims are in form for allowance and action to that end is respectfully requested.

Respectfully submitted,

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